Thus, Applicants have deleted the subject matter encompassed by the non-elected claims. Only claims drawn to crystals of Val-8 GLP-1(7-37)OH and compositions thereof are under consideration.

The Examiner noted that the declaration filed in response to the last office action dated July 7, 2000 was persuasive. Furthermore, the Examiner stated that "[c]laims rewritten commensurate in scope with the scope of the Declaration will be considered for allowance." Applicant asserts that the amended claim set presented above is fully supported by the Declaration and addresses the Examiner's rejections as discussed below.

Rejection under 35 U.S.C. §112, first paragraph
Written Description

The Examiner rejected Claims 33-43 under 35 U.S.C. §112(1) as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The rejection is specifically directed at a lack of written description for Val-8-GLP-1 crystals made from a solution comprising a monosaccharide or disaccharide.

The Revised Interim Guidelines indicate that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. The revision does not require a particular number of species to support a genus, but rather requires that the species adequately described be representative of the claimed genus. Revised Interim Guidelines for Examination of Patent Applications under 35 U.S.C. Sec. 112, para. 1 "Written Description" Requirement; Request for Comments, 64 Fed. Reg. 71427 (1999). The Guidelines also provide that there is a "strong presumption that an adequate written description of the claimed invention is present when the application is filed." *Id.* at 71434. Furthermore, the Guidelines state that "[t]he examiner has the initial burden . . . of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention

provides support for the claims. *Id.* at 71435.

Applicants respectfully assert that the application as filed provides more than an adequate written description of Val-8-GLP-1 crystals made from a crystallization solution containing a monosaccharide or disaccharide. On page 3, line 18 of the Specification the inventors state that "tetragonal flat rod shaped or plate-like crystals . . . could be reproducibly formed from a mother liquor containing a GLP dissolved in a buffered solution and . . . a mono or disaccharide, over a wide range of pH conditions." On page 12, line 3, the Specification provides that "mono or disaccharides may be substituted for the alcohol in the same ratios on a weight to volume basis." A list of mono and disaccharides suitable for use in making the crystals of the present invention is also provided.

Finally, there are <u>two</u> specific examples wherein Val-8-GLP-1 crystals are made using a monosacchardie or disaccharide. Example 9 on page 22 provides a protocol to make crystals with 5% trehalose (a disaccharide). On line 18, the inventors state that "[a]fter 24 hours V8-GLP-1 crystal clusters and single rectangular crystals were identified." Measurements of these crystals is also provided. Example 10 on page 23 provides a protocol to make crystals with 10% mannitol (a monosaccharide). After 24 hours small rectangular plate-like crystals were identified. Thus, Applicants have not only described a genus of mono and disaccharides that can be used to make the crystals of the present invention, but have also reduced to practice crystals made using both a monosaccharide and a disaccharide at different concentrations (5% and 10%).

Although Applicants assert that the written description in the Application support claims to crystals made using any mono or disaccharide, Applicants have amended the claims to limit the crystallization solution to a specific concentration range of mono or disaccharide as well as to the specific list of mono and disaccharides described in the Specification. The concentration range is supported by the disclosure on page 12, line 3. The disclosure provides that mono and disaccharides

may be substituted for ethanol and used in the same ratio as ethanol on a weight to volume basis. On page 11, line 23, the preferred concentration range of 2-15% and 3-13% (v/v) is provided for the alcohol component. Claims 53, 54, and 55 are directed to crystals made using a mono or disaccharide. Claim 53 specifies the concentration range of 2-15% and contains a Markush group with select mono or disaccharides. Claim 54 and Claim 55 are limited to trehalose and mannitol, respectively.

The mono and disaccharides specified in this Markush group contain monosaccharides with 4 to 6 carbons and some closely related disaccharides. The law does not require that the Applicant reduce to practice every mono or disaccharide to support a claim encompassing a genus of these sugars. Examples are provided using both a mono and disaccharide to make crystals. This is "representative" of the 10 sugars specified in the claim. Furthermore, the Examiner has not presented any evidence as to why the Examples and other disclosure discussed above does not adequately describe crystals made using mono and disaccharides.

Rejection under 35 U.S.C. §112, first paragraph

Enablement

The Examiner rejected Claims 33-43 and 46 under 35 U.S.C. §112(1) because "the specification, while being enabling for using ethanol or propanol as the crystallization solution, does not reasonably provide enablement for a mono or a disaccharide in the crystallization solution as claimed." Although enablement is a separate statutory requirement distinct from the written description requirement, many of the comments discussed above are applicable to an analysis of enablement.

The Federal Circuit has held that a patent specification complies with the enablement requirement as long as "undue experimentation" is not required to practice the invention. *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988). The court has set forth a number of factors to consider in deciding whether a disclosure would require undue experimentation. These factors include:

1) the quantity of experimentation necessary;

2) the amount of direction or guidance presented;
3) the presence of absence of working examples;
4) the nature of the invention;
5) the state of the prior art;
6) the relative skill of those in the art;
7) the predictability or unpredictability of the art; and
8) the breadth of the claims.

Id.; *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362 (1999). Applicants respectfully traverse the Examiner's rejection. The Specification provides two working examples as well as a list of different sugars that are suitable to make the crystals of the present invention. The claims (as amended) provide a concentration range of 2 to 15% (weight to volume) of mono or disaccharide. Two different examples are provided which set forth protocols using two different concentrations of sugar (Example 9, 5% trehalose; Example 10, 10% mannitol) that are within this specified concentration range. It would not be undue experimentation to vary the amount of mono or disaccharide within the specified range to determine what concentrations are optimal with respect to other characteristics of the crystallization solution such as polarity, ionic strength, or pH.

The Examiner suggests that the use of mono or disaccharides in the crystallization media would alter the characteristics of the crystallization media and effect the conformation of the protein being crystallized. Examples 9 and 10 clearly show that mono and disaccharides can be used in place of ethanol to make the crystals. The Examiner presents no evidence supporting the proposition that there is likely to be a differential effect using mono and disaccharides other than trehalose and mannitol on Val-8-GLP-1 protein conformation.

Applicants assert that claims 53-55 which provide a concentration range as well as a list of specific mono and disaccharides are enabled.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claims 33-43 and 46 as being indefinite. The Examiner points out that the nature of the

solvent is not specified. Thus, independent Claims 43 and 57 each provide the limitation that the solution is an "aqueous" solution. The Examiner also asserts that the term v/v or w/v are indefinite with respect to what the amounts are compared with. Thus, the claims have been amended to specify that v/v is volume as a percent of total volume and w/v is weight as a percent of total volume.

Claim 40 has been rewritten as two different composition claims and Claims 43 and 46 have been deleted; thus, the Examiner's indefiniteness rejection of these claims is no longer relevant.

Summary and Conclusion

In view of the remarks and amendments provided herein above, it is respectfully submitted that the rejections have been overcome. The claims amendments presented above do not add new matter. Entry of the amendment, reconsideration and withdrawal of the rejection are therefore requested.

If the Examiner feels that a telephone conversation with Applicants' Attorney would be helpful in expediting the prosecution of this case, the Examiner is urged to call Applicants' Attorney at (317)276-0280.

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October 20, 2000